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Two types of experiments are described. The first was directed at the neurochemical systems that control the activity of brain serotonergic (dorsal raphe nucleus) neurons. The second examines the effects of serotonin and norepinephrine on the activity of target neurons carrying out sensory information processing or motor function. Both sets of studies utilize single unit activity in combination with multibarrel microiontophoresis in awake animals. This research program provides critical links for understanding both the control of brain neurochemical systems and the control exerted by them. This will help to elucidate, more broadly, the role of these modulatory brainstem neurochemical systems in processes such as state-dependent changes in physiology and behavior, and arousal and attention.

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9 JUL 1992

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June 30, 1992

Dr. Genevieve Haddad
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Bolling Air Force Base, DC 20332-6448

Dear Dr. Haddad:

The brief narrative in this letter constitutes my Annual Technical Report for my AFOSR grant (90-0294). I have previously sent you copies of relevant papers and manuscripts.

The goal of our AFOSR research is to take the next logical step in our understanding of the function of modulatory chemical neurotransmitters in the mammalian brain. Prior to this, we and others had gathered a great deal of information about the electrophysiological activity of brainstem monoaminergic (serotonergic, noradrenergic, and dopaminergic) neurons. Additionally, a great deal of information was known about the action of these neurotransmitters upon the activity of their postsynaptic target neurons, such as those in the cerebral cortex.

Within this context, we are asking two fundamental questions. First, what are the neurochemical afferents that control the activity of the monoaminergic neurons themselves? For example, we know that serotonergic neurons can be activated by phasic sensory stimuli, and that they dramatically decrease their activity during sleep. However, we have no information regarding the neurochemical inputs that mediate these increases and decreases in neuronal activity. Second, although we have a general sense of how norepinephrine and serotonin influence their target neurons, the critical issues of how and when this occurs under physiological conditions remains obscure.

We address these questions by bringing together two well-known approaches that typically have been used separately: microiontophoresis and single unit recordings in conscious animals. Specifically, we examine extracellularly recorded action potentials in combination with the microiontophoretic application of neurotransmitter agonists or antagonists in awake, head-restrained cats. This allows us to examine questions in the absence of any confounding influences of anesthesia, and to ask these questions in the intact animal under physiologically-relevant conditions.

We have made substantial progress on the first issue and have written two manuscripts on this work (one a methodological paper, in press, and, the other, an empirical report of the results, also in press in J. Neurosci.). We found that we could block the activation of serotonergic neurons by phasic sensory stimuli through the iontophoretic application of excitatory amino acid (EAA) antagonists. Importantly, these effects were seen in the absence of any change in the spontaneous or basal activity of these neurons. We also found that we could restore the decreased activity of a serotonergic neuron during sleep to its waking level by iontophoretically applying a GABA antagonist. Once again, the specificity of this effect is demonstrated by the fact that the same amount of antagonist had no neuronal effect when applied during waking. Thus, these data indicate that under

physiologically relevant conditions an EAA input can be activated by phasic sensory stimuli and thereby increase the discharge of serotonergic neurons, while a tonic GABAergic input exerted during sleep can suppress the activity of these neurons.

Experiments on the second issue are just beginning to bear fruit. We believe that this will be the next productive line of research in our laboratory. We are asking two separate questions. First, we want to know how the activity of somatosensory neurons in the cat cortex, which are normally activated by movement of muzzle whiskers, can be modulated by variables such as behavioral state, arousal, and attention, and further, what neurochemical afferent inputs mediate these changes. Second, we want to know how the activity of motoneurons that control jaw movements (MoV) can be modulated by behavioral and environmental factors, and what neurochemical afferent inputs mediate these changes. These studies are similar to those described above, where we determined which neurochemical inputs were exerting their effect upon serotonergic neurons by microiontophoretically applying neurotransmitter agonists and antagonists during specific environmental or physiological conditions, however, they are one synapse further along in the circuitry.

I hope you find these materials useful. I look forward to continued interactions with you and Dr. Berry, and thank you for your continued support of our research program.

Sincerely,

Barry L. Jacobs
Professor and Director
Program in Neuroscience

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